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EFFECTS OF PIONS ON NORMAL TISSUES

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INTRODUCTION

Pions, an intermediate-LET radiation, bear complex physical characteristics which depend on beam dimensions. For therapeutic application of pion beams, the Bragg peak must be spread out to encompass the treatment volume, and the range must be modulated to produce a uniform biological effect across the peak. The LET variation across the modulated peak must also be considered in terms of providing a uniform biological effect when fractionated schemes are employed. Verification of the uniform biological effectiveness of beams of various dimensions produced at LAMPF has been made using cultured mammalian cells[1] and mouse jejunum.[2] The latter is of more clinical relevance since fractionated doses of pions are used.

The contribution of charged particles and fast neutrons resulting from pion capture in tissue and the dependence of this contribution on pion treatment volume are another aspect to be considered[3] and are discussed in detail in this workshop.[4,5,6] The role of fast neutrons becomes significant for larger pion treatment volumes. The volume dependent RBE differences have been estimated by using cultured mammalian cells.[5,6] Our preliminary study using the mouse jejunum also indicates that fractionated treatment appears to result in a higher RBE value for large treatment volumes if the peak width remains the same.

In addition to the characterization of pion beams as a part of pretherapeutic radiobiology studies, RBE measurements in normal tissues, particularly for late effects, are of considerable importance since the normal tissue tolerance is often determined by its late effects.

In this paper, normal tissue radiobiology studies at LAMPF are reviewed with regard to: (1) biological beam characterization for the therapy programs and (2) the current status of acute and late effect studies using rodents.

A. Radiobiological Characterization of Pion Therapy Beams

(1) Verification of biological effectiveness at two different peak positions

Mice in a water phantom were exposed to four pion dose fractions of hi

intervals between fractions) at the proximal and distal peak positions of a modulated 14 cm peak width beam (Fig. 1). Using the intestinal crypt survival assay as described by Withers and Elkind,[7] the results plotted as a function of the proximal peak dose indicated that the biological effects at both peak positions were similar (Fig. 2). This study confirmed that the modulation of the pion beam was appropriate.[2] It suggests that the RBE at the distal position is approximately 16% higher than at the proximal position.

(2) RBE variations for beams of small versus large peak width

A similar study was made to determine if variation in RBE exists for clinical beams of large (14 cm) or small (6 cm) peak width but having equal field size of 11 cm x 14 cm. Mice were given four pion dose fractions (3 hr intervals between fractions) at the mid peak position of the beams (Fig. 3). The intestinal crypt survival data showed no significant differences in biological effects for these two beams as shown in Fig. 4.[2]

(3) Volume Effects

Two beams of an 8 cm peak width but of different field sizes, 7.5 cm x 7.5 cm or 20 cm x 20 cm (full width at half maximum), were tested using the mouse jejunum for one and four pion dose fractions given at the mid peak position.

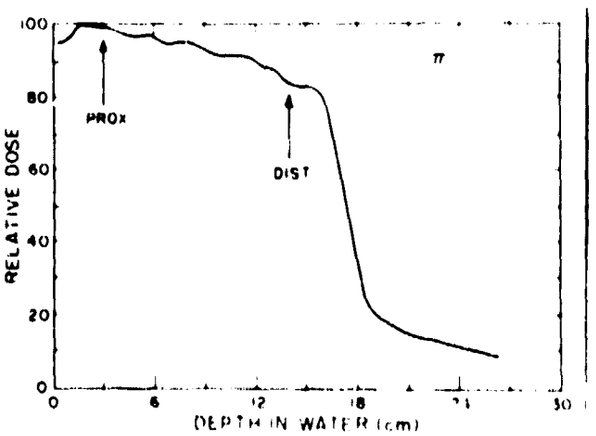

Fig. 1. Dose distribution curve of a 14 cm peak width beam in a water phantom. The beam size was 11 cm x 14 cm. The arrows indicate the positions at which mice were exposed to pions. Note that the distal peak dose is approximately 16 less than the proximal dose (Figure modified from Ref. 2).

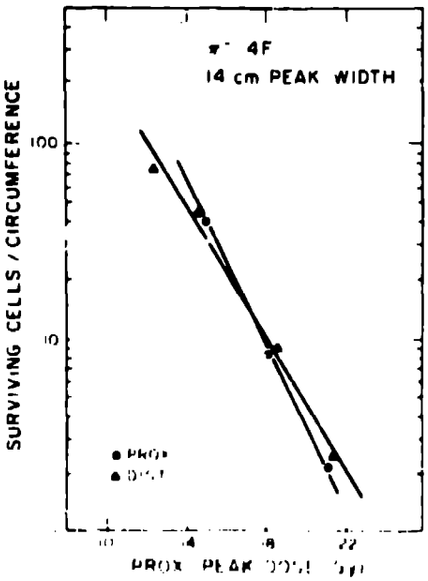

Fig. 2 The intestinal crypt cell survivals for 4 pion dose fractions expressed as a function of the proximal peak dose (Figure modified from Ref. 2).

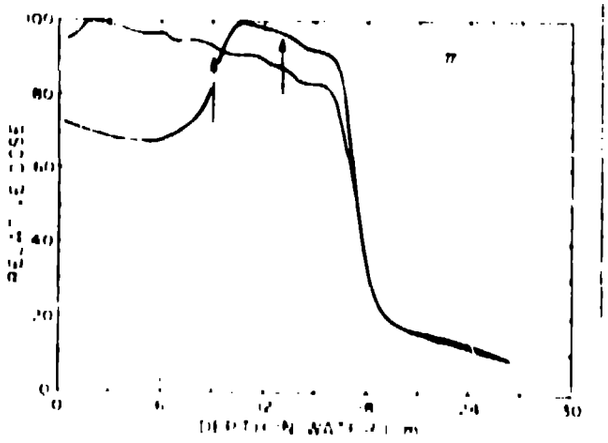

Fig. [illegible] distribution curves of large (14 cm) and small (6 cm) peak beams with [illegible] (Figure modified from Ref. 2).

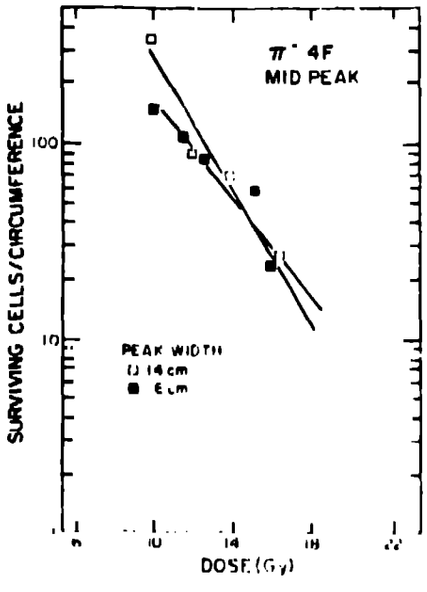

Fig. 4. The intestinal crypt cell survivals for 4 pion dose fractions expressed as a function of the dose for the two beams of different peak width which are described in Fig. 3 (Figure modified from Ref. 2).

The dose rate was 0.1-0.12 Gy/min for the large beam and 1.6 Gy/min for the small beam. Our preliminary data indicate that at four fractions the biological effect is greater for the large beam compared to the small beam despite the fact that the dose rate for the large beam is considerably lower than that for the small beam. No differences in biological effects, however, are observed at single fractions as shown in Fig. 5.

B. RBE Measurements

RBE measurements with pions for various normal tissues at LAMPF have, so far, been made using beams with narrow peak widths because of limited dose rate in the past. The RBE values of such beams may be different from beams used clinically due to differences in LET, thus limiting the use of such data for the clinical program. The RBE data available to date were compiled for acute effects on mouse skin,[8] mouse jejunum,[9,10,10] and for late effects on the mouse kidney,[11] rat spinal cord[12] and rat colon[13] as shown in Fig. 6 and Table 1. The RBE values are, in general, best-fitted by a power function when the RBE is plotted as a function of dose per fraction. The slopes for late

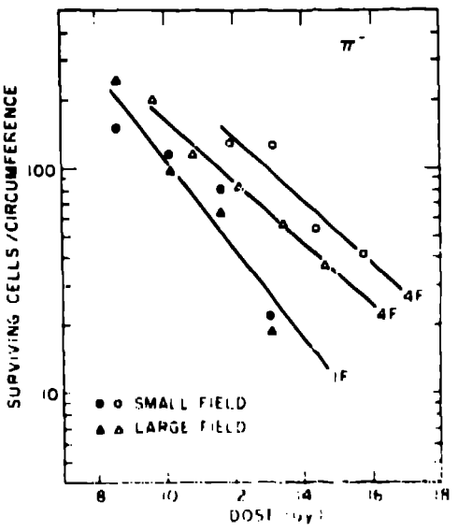

Fig. 5. Effect of beams of 8 cm peak width but different field sizes (7.5 cm x 7.5 cm and 20 cm x 20 cm) on survival of intestinal crypt cells following 1 and 4 pion dose fractions.

TABLE 1

PARAMETERS FOR RBE VALUES EXPRESSED AS A FUNCTION OF DOSE PER FRACTION

$$RBE = K\,D^{-S}$$

Tissues	Beam Size	K	S	Ref.
Skin	3 cm	1.97	0.20	(8)
Jejunum	3 cm	1.98	0.24	(9)
Jejunum	4 cm	1.43	0.12	(10)
Jejunum	14 cm	2.04	0.27	(2)
Kidney	3 cm	2.46	0.33	(11)
Spinal Cord	2 cm	3.69	0.33	(12)
Colon	2 cm	3.66	0.38	(13)

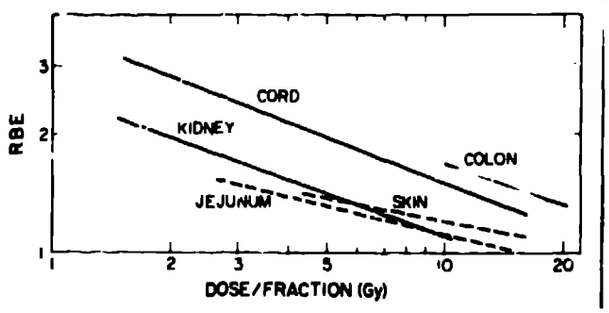

Fig. 6. RBE values plotted as a function of dose per fraction. Solid lines for late effects and dotted lines for acute effects. Sources: Skin,[8] Jejunum,[9] Kidney,[11] Spinal Cord,[12] and Colon.[13]

effects appear to be steeper compared to those for acute effects. For example, at clinically relevant dose fraction regions, the RBE value for the jejunum (acute effect) is considerably less than that for the spinal cord (late effect).

When the values for repair per dose fraction (fractional repair) were compared, the data suggest that the fractional repair is considerably less for pions compared to X rays regardless of tissue studied (Table [illegible]). Further, the fractional repair ratios (pions/X rays) also appear to vary depending on tissue, fraction number as well as beam tune. At five fractions, this ratio for mouse skin, for example, is 0.55 ± 0.11 and that for jejunum is [illegible]. As the number of fractions increases, the fractional ratio for acute effects seems to decrease, whereas, that for the kidney late effect appears to increase.

DISCUSSION

Prelinical radiobiology studies required for the therapy program are designed for (1) verify the uniformity of biological effect across the peak; (2) provide RBE data for beams of various dimensions; and (3) provide RBE data for acute and late effects of [illegible]. [illegible] large clinical beam tunes using fractionated schemes, the [illegible] the appropriate experimental system since the exposure [illegible] affect the final outcome. [illegible] quality of radiation. In addition, if [illegible] of the body of the animal, the effect of neutrons [illegible] must also be taken into consideration.

TABLE 2

COMPARISON OF FRACTIONAL REPAIR VALUES[a] FOR X RAYS AND PIONS

		Number of Fractions					
Tissues		2F	4F	5F	10F	15F	Ref.
Skin	X	0.59		0.57			(8)
	Pi	0.39		0.37			
Jejunum	X	0.45		[illegible]			(9)
	Pi	[illegible]		[illegible]			
Jejunum	X		[illegible]		0.44		(10)
	Pi		[illegible]		[illegible]		
Jejunum	X		[illegible]				[illegible]
	Pi		[illegible]				
Kidney	X	[illegible]		[illegible]		[illegible]	[illegible]
	Pi	[illegible]		[illegible]		[illegible]	
[illegible]	X			[illegible]		[illegible]	[illegible]
	Pi			[illegible]		[illegible]	
[illegible]	X	[illegible]					
	Pi	[illegible]					

[a] [illegible]

A comprehensive review [illegible] reported previously[14] [illegible] are required to confirm this phenomenon.

[illegible]

tissues, particularly for late effects, are required to obtain a better understanding of optimal pion fractionation schemes. Such efforts on the late effect studies of normal tissues (spinal cord, lung, kidney, liver, colon and lens in rodents) are in progress through collaborations at Los Alamos.

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